

REMARKS

The claims have been rejected under 35 U.S.C. §112. The claims have been amended to obviate the rejection.

Claims 1 and 8-18 and 20 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Elango et al., U.S. 4,981,995 in view of Chaudhari et al., U.S. Patent No. 6,093,847.

The Examiner's rejection is respectfully traversed.

As now amended, the claims are directed to an improved process for the preparation of 2-aryl propionic acids. The process comprises the steps of reacting an aryl compound, an organic acid having essentially less than 6% water by volume and a palladium catalyst in an organic solvent at a temperature ranging from 30 to 130°C, for a period ranging between 0.3 to 4 hours, at pressures ranging between 50 to 1500 psig. The mixture is then cooled to an ambient temperature. Next, the reaction vessel is flushed with an inert gas and the solvent is removed by conventional methods. The catalyst is separated and the 2-aryl propionic acid is isolated.

On the other hand, Elango et al., '995 is directed to a process for carbonylation of IBPE to prepare Ibuprofen. Ibuprofen is one of the compounds falling under the category of 2-aryl propionic acids. However, the phrase 2-aryl propionic acid represents a broader category, including many compounds such as Flurbi-profen, Ibuprofen, keto-profen and Naproxen. Elango et al. '995, merely teaches the process of forming one of the aforementioned compounds and does not teach or suggest the process being adapted to be suitable for preparing other compounds in the group. On the other hand, the Applicants' present invention includes a

process for carbonylation of IBPE to prepare a number of 2-aryl propionic acids. Thus, the Applicants' process is not only capable of preparing Ibuprofen but also other 2-aryl propionic acids such as Flurbi-profen, keto-profen and Naproxen. A person skilled in the art, would not be able to read Elango et al. '995 and prepare compounds other than Ibuprofen without undue experimentation.

Elango et al. '995 also teaches a process wherein preparation of Ibuprofen from IBPE is carried out in a multiphase manner. More particularly, according to Elango et al., as seen in examples 4 and 9, during the process of preparing Ibuprofen, an organic layer and an aqueous layer are formed which are thereafter separated. Additionally, in Elango et al., the IBPE is reacted with CO in an acidic aqueous medium containing at least 10% of H₂O based on the weight of IBPE. Elango et al. also teaches that dissociated hydrogen and chloride ions are essentially derived from hydrogen halide such as HCl/HBr.

The presence of water in an amount in excess of 10% based on the weight of IBPE simultaneously along with an acid such as HCl/HBr will only tend to form a bi-phasic system wherein the promoters and water form a separate aqueous phase and the catalyst and IBPE form an organic phase. Thus, the presence of water in an amount in excess of 5% will tend to form a bi-phasic system.

On the other hand, the Applicants' invention teaches a process for preparation of 2-aryl propionic acid in a homogeneous phase. This is because the Applicants have determined that the preparation of 2-aryl propionic acid in a homogeneous phase from the reactants is more beneficial in terms of percent selectivity and percentage conversion. The Applicants have noticed that percentage selectivity and percentage conversion are about 20% to 29% higher when 2-aryl propionic acids are prepared in a homogenous phase as compared to a bi-phasic

system. Thus, the main target of the Applicants' was to approach a homogeneous system wherein the reaction is ideally carried out in a strictly anhydrous condition. A strictly anhydrous condition is very difficult to achieve and thus the Applicants have found that the amount of water should be less than 6%. If the amount of water present exceeds 6% a bi-phasic system is formed, which eventually leads to a decrease of percentage selectivity and percentage conversion. Thus, the teaching of Elango et al. is directly in contradiction to the teachings of the present invention.

On the other hand, Chaudhari et al., '847 also teaches a process for carbonylation of IBPE to prepare Ibuprofen. Chaudhari et al. '847 merely teaches a process for preparing one of the aforesaid compounds of the 2-aryl propionic acid group and does not teach or suggest that the process be suitable for adapting for preparing other compounds in the aforesaid group. Again, the Applicants' process can prepare any number of products which fall within the group. It is respectfully submitted that the references cited by the Examiner only teach processes for preparing a particular compound whereas the present invention teaches a more simplified and generic process for preparing a number of 2-aryl propionic acids with high percentage conversion and selectivity.

Additionally, when reading Chaudhari et al., '847, one will not be in a position to prepare compounds other than Ibuprofen without undue experimentation. The Chaudhari '847 reference describes a process of preparing Ibuprofen from 2-aryl alcohol using a very specific catalyst comprising group VIII metal and semiliable chelating ligand containing an "N" donor and an "O" group. The semiliable chelating agent imparts efficacy to the performance of the compounds used in the process. On the other hand, the catalyst used in the Applicants' invention may comprise different types of palladium compounds which can act like a catalyst.

In the Applicants' invention, the process can be achieved wherein different types of catalysts can be used interchangeably without affecting the percentage selectivity and percentage conversion.


Additionally, the Applicants' believe that the teachings of Elango et al. '995 and Chaudhari et al. '847 cannot be combined as Elango '995 teaches a process for preparing Ibuprofen in a bi-phase system, whereas Chaudhari '847 teaches a process for preparing Ibuprofen in a homogeneous system. More specifically, Elango '995 teaches that IBPE is reacted with CO in an acidic aqueous medium containing at least 10% of water based on the weight of IBPE and Chaudhari et al. '847 teaches that water should be at least up to 6% weight based on IBPE. It is well established that in order to combine the teachings of two references there should be a reasonable expectation of success and there must be some motivation to combine the two citations. In this instance, there is no motivation to combine the references as Elango '995 teaches that the amount of water added during the reaction should be at least 10% and better results are obtained when the amount of water is increased. However, to the contrary, Chaudhari et al. '847 teaches that the amount of water in the reaction should not exceed 6%. Chaudhari et al., '847 additionally continues to state that if the amount of water exceeds 6%, the percentage selectivity and percentage conversion is decreased. Thus, there is no motivation to combine the reference nor can they technically be combined to obtain the Applicants' invention. Not only can the teachings not be easily combined, both references are only directed to preparing only Ibuprofen and not any of the other 2-aryl propionic acid derivatives.

In view of the foregoing, the Applicants contend that the amended claims and the claims dependent therefrom are in proper form. Applicants also respectfully contend that the

teachings of Elango et al. '995 in view of Chaudhari et al. '847 do not establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Thus, claims 1, 2 and 8-21 are considered to be patently distinguishable over the prior art of record.

The application is now considered to be in condition for allowance, and an early indication of same is earnestly solicited.

Respectfully submitted,



Arlene J. Powers
Registration No. 35,985
Gauthier & Connors, LLP
225 Franklin Street, Suite 3300
Boston, Massachusetts 02110
Telephone: (617) 426-9180
Extension 110